PATENT ABSTRACTS OF JAPAN

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(54) GELATIN FILM COMPOSITION AND READILY SOLUBLE HARD GELATIN CAPSULE

(57)Abstract:
PURPOSE: To obtain a hard capsule having sufficient mechanical strength, applicable to various medicines and capable of withstanding the formulation without raising problems such as insolubilization by reaction with a special medicine even in filling the special medicine therein and thereby imposing any limitation on contents.
CONSTITUTION: The objective hard capsule is obtained by adding and blending polyethylene glycol with a gelatin raw material consisting essentially of succinylated gelatin and forming the resultant blend. Thereby, a medicine which has hither been difficult to formulate such as a macrolide-based antibiotic substance can be encapsulated.

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* NOTICES *

CLAIMS

[Claim(s)]
[Claim 1] A gelatin coat constituent which uses as a principal component a gelatin raw material whose 50 – 100 % of the weight is amber–ized gelatin, and is characterized by carrying out addition combination of the polyethylene glycol at this.
[Claim 2] A soluble hard gelatine capsule formed from a coat constituent according to claim 1.

[Translation done.]

* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] When this invention is further explained in full detail about a new gelatin coat constituent and a soluble hard gelatine capsule, it relates to the gelatin coat constituent which blended the polyethylene glycol with the gelatin raw material which used amber-ized gelatin as the base and which is excellent in collapsibility and can moreover prevent embrittlement, and a soluble hard gelatine capsule.
[0002]
[Description of the Prior Art] Conventionally, as a material for hard capsules, gelatin is used as a base material and what added plasticizers, such as a glycerol or a sorbitol, to this is known (henceforth an ordinary gelatine capsule).
[0003] However, it is in the ordinary gelatine capsule formed from such a material, The defect of not collapsing in the decay time which it was admitted that this reacted easily with the amino group of the gelatin which constitutes a capsule, and formed a macromolecule in being the drug which contains especially aldehyde groups, such as a macrolide, when those capsule contents are special drugs, for example, and un-arranging [which it is called insolubilization of a capsule] arose by formation of this macromolecule, as a result was set to the Japanese pharmacopoeia will be invited. Especially the thing that such a phenomenon produces when a long-term accelerated test is performed on condition that 40 degrees C indispensable to the manufacturing license application of drugs and 75%RH is a big problem.
[0004] Then, this invention persons have proposed previously the soluble hard capsule which used amber-ized gelatin as a capsule base material so that they may improve such a defect (JP,61-186314,A).
[0005] However, when this capsule has a low mechanical strength and is filled up with a drug compared with an ordinary gelatine capsule, at present, it is difficult to put in practical use because of the defect that a capsule coat tends to break at the time of conservation with the passage of time.
[0006] In this invention, it was made in view of the above-mentioned situation. Therefore, even if filled up with a special drug, the problem of react with this and insolubilize be produced, therefore contents be restricted, but it can apply to various drugs, and aim at offer the soluble hard gelatine capsule formed with the gelatin coat constituent and this constituent which used as the base the amber-ized gelatin which can ** a hard capsule with sufficient mechanical strength which can moreover be equal to pharmaceutical preparation-ization.
[0007]
[Means for Solving the Problem and its Function] this invention persons found out that a mechanical strength of an amber-ized gelatine capsule obtained could be raised by carrying out addition combination of the polyethylene glycol to a coat constituent which uses amber-ized gelatin applicable to various drugs as the base so that a property may not change with reactions with a contents drug, as a result of inquiring wholeheartedly, in order to attain the above-mentioned purpose. Namely, in case a hard gelatine capsule is **(ed) from a gelatin raw material which uses amber-ized gelatin as a principal component In a gelatin raw material, a polyethylene glycol and by carrying out addition combination of the polyethylene glycol of molecular weight 1000-20000 preferably As [insolubilize / even if it is the drug which has

aldehyde groups, such as a macrolide,] It is what completed a header and this invention for a new hard gelatine capsule which has a good mechanical strength which may be adapted for various drugs good, and moreover has good collapsibility and solubility, and usually exceeds a gelatine capsule being obtained. It is.

[0008] in addition, blending a polyethylene glycol with an ordinary gelatine capsule is already known -- **** (JP,3-80930,A, JP,4-159218,A) -- a thing usually concerning [these proposals] a gelatine capsule -- it is It is not a thing about a hard filled capsule which exists and uses amber-ized gelatin as the base. Moreover, an improvement of brittleness under low content moisture of a coat [in / usually / in combination of the above-mentioned polyethylene glycol / a gelatine capsule], It is not a thing aiming at improvement in reinforcement of a hard filled capsule which restoration pharmaceutical preparation-ization of an unstable drug is attained, or aims at preventing that a gelatine capsule usually adheres by container or capsules to moisture, and uses amber-ized gelatin as the base, either. Giving good collapsibility, solubility, and a mechanical strength by blending a polyethylene glycol with a hard filled capsule which uses amber-ized gelatin as the base, having fitted a hard filled capsule of the amber-ized gelatin base to various drugs, and having enabled practical use of it starts this invention person's new knowledge.

[0009] Therefore, this invention uses as a principal component a gelatin raw material whose 50 - 100 % of the weight is amber-ized gelatin, and offers a soluble hard gelatine capsule formed in this from a gelatin coat constituent characterized by carrying out addition combination of the polyethylene glycol, and this gelatin coat constituent.

[0010] Hereafter, lessons is taken from this invention and it explains in more detail. As a gelatin coat constituent of this invention was mentioned above, addition combination of the polyethylene glycol is carried out at a gelatin raw material which uses amber-ized gelatin as a principal component, and a soluble hard gelatine capsule of this invention is formed from this coat constituent.

[0011] A gelatin raw material which contains the above-mentioned amber-ized gelatin here, amber-ized gelatin -- although it may be independent or you may be the mixture of amber-ized gelatin and usual gelatin, as for amber-ized gelatin, it is desirable to consider as mixture of amber-ized gelatin and usual gelatin, when low cost-ization is desired, since it is usually more expensive than gelatin, and a content of amber-ized gelatin is used as 50% of the weight or more of a gelatin raw material in this case -- having -- especially -- It is desirable to consider as 70 % of the weight or more. There is a possibility that the solubility of a capsule may deteriorate that a content of amber-ized gelatin is less than 50 % of the weight depending on a class of capsule contents. In addition, amber-ized gelatin can be easily obtained by making a succinic anhydride react to gelatin.

[0012] Although especially a polyethylene glycol that carries out addition combination is not restricted to this gelatin raw material, since the solubility of a capsule and a mechanical strength can be raised notably, it is desirable to consider as molecular weight 1000-20000, and it is more desirable to mix and use one sort or two sorts or more of polyethylene glycols further chosen from molecular weight 1000, 1500, 1540, 4000, 6000, and 20000.

[0013] Although especially addition loadings of this polyethylene glycol are not restricted, receive the above-mentioned raw material gelatin. If a mechanical strength of a capsule obtained as it is appropriate to consider as 1 - 30 % of the weight and it is less than 1 % of the weight may not fully improve and, on the other hand, exceeds 30 % of the weight, while a gelatin solution will become cloudy, it becomes difficult for the viscosity to fall rapidly and to make homogeneity mix a polyethylene glycol, and there is a case where it becomes impossible to obtain a uniform capsule coat at the time of capsule shaping.

[0014] Although a gelatin coat constituent of this invention carries out addition mixing of the above-mentioned polyethylene glycol at the above-mentioned gelatin raw material, an addition mixing method of a polyethylene glycol can be performed in this case according to a conventional method. Water is added to a gelatin raw material, after it carries out natural neglect of this for several hours and it carries out water absorption swelling, specified quantity addition mixing of the polyethylene glycol can be carried out in the state of an

aqueous solution, viscosity can be adjusted, a jelly-like gelatin constituent can be obtained, and, specifically, a method of fabricating this with a conventional method can be illustrated. In addition, a food color, a titanium dioxide, etc. which were specified if needed by other additives, for example, Pharmaceutical Affairs Law, or Food Sanitation Law etc. in addition to the above-mentioned component can be added like a case where the conventional hard gelatine capsule is **(ed) in this case.

[0015] In addition, although a gelatin coat constituent of this invention is preferably used as a charge of an encapsulant in the drugs field, it is not limited to this, but can be suitably used as a container material or covering material also in various fields, such as quasi drugs, cosmetics, food, and the miscellaneous-goods field, and can add a proper additive according to that use in this case.

[0016] Moreover, even if filled up with a drug with a special drug which has an aldehyde group, a problem of reacting with this and insolubilizing is not produced, therefore contents are not restricted, but a hard gelatine capsule formed from this gelatin coat constituent can be applied to various drugs, and it has sufficient mechanical strength which can moreover be equal to pharmaceutical preparation-ization.

[0017]

[Example] Although an example is shown and this invention is explained concretely hereafter, this invention is not restricted to the following example.

[0018] Natural neglect of the 13.5l. of the purified water was added and carried out for about 1 to 2 hours, and it carried out water absorption swelling to [example 1] amber-ized gelatin 7.5kg. After gelatin fully swells, it warms and agitates at 60 degrees C, gelatin was dissolved in homogeneity, after having added 1.5kg (10-% of the weight concentration) of 50-% of the weight aqueous solutions of the polyethylene glycol of molecular weight 4000, agitating and adjusting that viscosity into this gelatin solution further, degassing processing was carried out with the conventional method, and the jelly for capsule shaping was obtained. This jelly was taught to capsule shaping equipment and the capsule of size No. 2 was fabricated.

[0019] Six kinds of capsules of size No. 2 were fabricated like the example 1 except having replaced with the polyethylene glycol of the [example 2] molecular weight 4000, and having made the addition of this polyethylene glycol into 1 % of the weight, 3 % of the weight, 5 % of the weight, 10 % of the weight, 20 % of the weight, and 30 % of the weight using the polyethylene glycol of molecular weight 6000.

[0020] Subsequently, the next experiment was conducted about the capsule obtained in the above-mentioned examples 1 and 2.

[Experiment -1] (evaluation to the crack of an empty capsule)

About the capsule obtained in the above-mentioned examples 1 and 2, gas conditioning was carried out so that the content moisture content of the coat might become just over or below 10%, and crack nature was investigated by the **** examining method (49.7g weight is dropped from a height of 10cm). Moreover, crack nature was similarly evaluated about the conventional amber-ized gelatin hard filled capsule and conventional common gelatin hard filled capsule (Japanese station capsule) which do not contain a polyethylene glycol as a comparison. A result is shown in a table 1. In addition, crack nature performed the above-mentioned **** trial about each 50 capsules, and evaluated it by the number which the crack produced.

[0021]

[A table 1]

実施例1により製造したカプセル

	割れテスト	カプセル水分
本発明品	6個	8.7%
公知のコハク化ゼラチン硬カプセル	48個	10.1%
普通ゼラチン硬カプセル	31個	10.1%

実施例2により製造したカプセル

	PEGの添加量（重量W%）	割れテスト	カプセル水分
本発明品	1	11個	10.1%
	3	5個	10.0%
	5	0個	10.0%
	10	0個	9.8%
	20	0個	9.7%
	30	3個	9.5%
公知のコハク化ゼラチン硬カプセル		48個	8.7%
普通ゼラチン硬カプセル		31個	10.5%

[0022] From the result shown in a table 1, the hard gelatine capsule concerning this invention could not break easily compared with the well-known amber-ized gelatin hard filled capsule and the ordinary gelatin hard filled capsule, and excelling in a mechanical strength was checked.

[0023] [Experiment -2] (collapsibility at the time of being filled up with a macrolide) this invention capsule manufactured in the example 1 was filled up with 250mg of midecamycin, and collapsibility was examined according to the term of the "capsule" of a publication to the twelfth amendment of a Japanese pharmacopoeia about this capsule. That is, after filling up the capsule immediately after manufacture with contents and leaving it for ten days on 60 degrees C and the conditions of 75% of relative humidity, the disintegration test was performed and time amount until a capsule carries out a opening from test initiation was measured. Moreover, the disintegration test was usually similarly performed about the gelatine capsule (Japanese station) as a comparison. A result is shown in a table 2. In addition, the data in a table is the average of six capsules.

[0024]

[A table 2]

	本発明品	比較品
開始時	25秒	1分11秒
10日後	24秒	開口せず

[0025] The capsule of this invention is excellent in collapsibility compared with a Japanese station gelatin hard filled capsule, moreover, this collapsibility does not almost have change after conservation with the passage of time, and it is admitted that the always stabilized collapsibility is shown so that clearly from the result of a table 2.

[0026] [Experiment -3] (solubility of an empty capsule)
According to the term of the "capsule" of a publication, the clarity-and-color-of-solution trial was carried out to the twelfth amendment of a Japanese pharmacopoeia about this invention capsule manufactured in the example 1. Moreover, the clarity-and-color-of-solution trial was usually similarly performed about the gelatine capsule (Japanese station) as a comparison. A result is shown in a table 3. In addition, the data in a table is the average of five capsules.

[0027]

[A table 3]

	溶融時間
本発明品	1分19秒
比較品	3分41秒

[0028] It was checked that the capsule concerning this invention excels [time amount / dissolution] in solubility short compared with a Japanese station gelatin hard filled capsule so

that clearly from the result of a table 3.
[0029]
[Effect of the Invention] As explained above, without producing decay delay with the passage of time, even if filled up with special contents which have an aldehyde group, such as a drug, the hard capsule which carried out the product made from a twist to the gelatin coat constituent of this invention has sufficient mechanical strength, and cannot produce un-arranging, such as a crack, easily, either. Therefore, it becomes possible [encapsulating the difficult drug] to manufacture medicine to the conventional capsules, such as a macrolide.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[Industrial Application] When this invention is further explained in full detail about a new gelatin coat constituent and a soluble hard gelatine capsule, it relates to the gelatin coat constituent which blended the polyethylene glycol with the gelatin raw material which used amber-ized gelatin as the base and which is excellent in collapsibility and can moreover prevent embrittlement, and a soluble hard gelatine capsule.

[Translation done.]

* NOTICES *

EFFECT OF THE INVENTION

[Effect of the Invention] As explained above, without producing decay delay with the passage of time, even if filled up with special contents which have an aldehyde group, such as a drug, the hard capsule which carried out the product made from a twist to the gelatin coat constituent of this invention has sufficient mechanical strength, and cannot produce un-arranging, such as a crack, easily, either. Therefore, it becomes possible [encapsulating the difficult drug] to manufacture medicine to the conventional capsules, such as a macrolide.

[Translation done.]

* NOTICES *

TECHNICAL PROBLEM

[Description of the Prior Art] Conventionally, as a material for hard capsules, gelatin is used as a base material and what added plasticizers, such as a glycerol or a sorbitol, to this is known (henceforth an ordinary gelatine capsule).
[0003] However, it is in the ordinary gelatine capsule formed from such a material, The defect of not collapsing in the decay time which it was admitted that this reacted easily with the amino group of the gelatin which constitutes a capsule, and formed a macromolecule in being the drug which contains especially aldehyde groups, such as a macrolide, when those capsule contents are special drugs, for example, and un-arranging [which it is called insolubilization of a capsule] arose by formation of this macromolecule, as a result was set to the Japanese pharmacopoeia will be invited. Especially the thing that such a phenomenon produces when a long-term accelerated test is performed on condition that 40 degrees C indispensable to the manufacturing license application of drugs and 75%RH is a big problem.
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[0005] However, when this capsule has a low mechanical strength and is filled up with a drug compared with an ordinary gelatine capsule, at present, it is difficult to put in practical use because of the defect that a capsule coat tends to break at the time of conservation with the passage of time.
[0006] In this invention, it was made in view of the above-mentioned situation. Therefore, even if filled up with a special drug, the problem of react with this and insolubilize be produced, therefore contents be restricted, but it can apply to various drugs, and aim at offer the soluble hard gelatine capsule formed with the gelatin coat constituent and this constituent which used as the base the amber-ized gelatin which can ** a hard capsule with sufficient mechanical strength which can moreover be equal to pharmaceutical preparation-ization.
[0007]

[Translation done.]

* NOTICES *

OPERATION

[Means for Solving the Problem and its Function] this invention persons found out that a mechanical strength of an amber-ized gelatine capsule obtained could be raised by carrying out addition combination of the polyethylene glycol to a coat constituent which uses amber-ized gelatin applicable to various drugs as the base so that a property may not change with reactions with a contents drug, as a result of inquiring wholeheartedly, in order to attain the above-mentioned purpose. Namely, in case a hard gelatine capsule is **(ed) from a gelatin raw material which uses amber-ized gelatin as a principal component In a gelatin raw material, a polyethylene glycol and by carrying out addition combination of the polyethylene glycol of molecular weight 1000-20000 preferably As [insolubilize / even if it is the drug which has aldehyde groups, such as a macrolide,] It is what completed a header and this invention for a new hard gelatine capsule which has a good mechanical strength which may be adapted for various drugs good, and moreover has good collapsibility and solubility, and usually exceeds a gelatine capsule being obtained. It is.

[0008] in addition, blending a polyethylene glycol with an ordinary gelatine capsule is already known -- **** (JP,3-80930,A, JP,4-159218,A) -- a thing usually concerning [these proposals] a gelatine capsule -- it is It is not a thing about a hard filled capsule which exists and uses amber-ized gelatin as the base. Moreover, an improvement of brittleness under low content moisture of a coat [in / usually / in combination of the above-mentioned polyethylene glycol / a gelatine capsule], It is not a thing aiming at improvement in reinforcement of a hard filled capsule which restoration pharmaceutical preparation-ization of an unstable drug is attained, or aims at preventing that a gelatine capsule usually adheres by container or capsules to moisture, and uses amber-ized gelatin as the base, either. Giving good collapsibility, solubility, and a mechanical strength by blending a polyethylene glycol with a hard filled capsule which uses amber-ized gelatin as the base, having fitted a hard filled capsule of the amber-ized gelatin base to various drugs, and having enabled practical use of it starts this invention person's new knowledge.

[0009] Therefore, this invention uses as a principal component a gelatin raw material whose 50 - 100 % of the weight is amber-ized gelatin, and offers a soluble hard gelatine capsule formed in this from a gelatin coat constituent characterized by carrying out addition combination of the polyethylene glycol, and this gelatin coat constituent.

[0010] Hereafter, lessons is taken from this invention and it explains in more detail. As a gelatin coat constituent of this invention was mentioned above, addition combination of the polyethylene glycol is carried out at a gelatin raw material which uses amber-ized gelatin as a principal component, and a soluble hard gelatine capsule of this invention is formed from this coat constituent.

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on a class of capsule contents. In addition, amber-ized gelatin can be easily obtained by making a succinic anhydride react to gelatin.
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[0014] Although a gelatin coat constituent of this invention carries out addition mixing of the above-mentioned polyethylene glycol at the above-mentioned gelatin raw material, an addition mixing method of a polyethylene glycol can be performed in this case according to a conventional method. Water is added to a gelatin raw material, after it carries out natural neglect of this for several hours and it carries out water absorption swelling, specified quantity addition mixing of the polyethylene glycol can be carried out in the state of an aqueous solution, viscosity can be adjusted, a jelly-like gelatin constituent can be obtained, and, specifically, a method of fabricating this with a conventional method can be illustrated. In addition, a food color, a titanium dioxide, etc. which were specified if needed by other additives, for example, Pharmaceutical Affairs Law, or Food Sanitation Law etc. in addition to the above-mentioned component can be added like a case where the conventional hard gelatine capsule is **(ed) in this case.
[0015] In addition, although a gelatin coat constituent of this invention is preferably used as a charge of an encapsulant in the drugs field, it is not limited to this, but can be suitably used as a container material or covering material also in various fields, such as quasi drugs, cosmetics, food, and the miscellaneous-goods field, and can add a proper additive according to that use in this case.
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[Translation done.]

EXAMPLE

[Example] Although an example is shown and this invention is explained concretely hereafter, this invention is not restricted to the following example.
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[0020] Subsequently, the next experiment was conducted about the capsule obtained in the above-mentioned examples 1 and 2.
[Experiment -1] (evaluation to the crack of an empty capsule)
About the capsule obtained in the above-mentioned examples 1 and 2, gas conditioning was carried out so that the content moisture content of the coat might become just over or below 10%, and crack nature was investigated by the **** examining method (49.7g weight is dropped from a height of 10cm). Moreover, crack nature was similarly evaluated about the conventional amber-ized gelatin hard filled capsule and conventional common gelatin hard filled capsule (Japanese station capsule) which do not contain a polyethylene glycol as a comparison. A result is shown in a table 1. In addition, crack nature performed the above-mentioned **** trial about each 50 capsules, and evaluated it by the number which the crack produced.
[0021]
[A table 1]

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実施例2により製造したカプセル

	PEGの添加量（重量W%）	割れテスト	カプセル水分
本発	1	11個	10.1%
	3	5個	10.0%
	5	0個	10.0%

明品	10	0個	9.8%
	20	0個	9.7%
	30	3個	9.5%
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[A table 2]

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[0027]
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[Translation done.]

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(54)【発明の名称】　ゼラチン皮膜組成物及び易溶性硬質ゼラチンカプセル

(57)【要約】

【目的】　特殊な薬物を充填してもこれと反応して不溶化するなどの問題を生じることがなく、従って内容物が制限されず、種々の薬物に適用し得、しかも製剤化に耐え得る十分な機械的強度を有した硬質カプセルを得る。

【構成】　コハク化ゼラチンを主成分とするゼラチン原料にポリエチレングリコールを添加配合し、これを成形して硬質カプセルを得る。

【効果】　マクロライド系抗生物質等の従来カプセル剤に製剤することが困難であった薬物をカプセル化することが可能となる。

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【特許請求の範囲】

【請求項１】　５０～１００重量％がコハク化ゼラチンであるゼラチン原料を主成分とし、これにポリエチレングリコールを添加配合したことを特徴とするゼラチン皮膜組成物。

【請求項２】　請求項１記載の皮膜組成物から形成された易溶性硬質ゼラチンカプセル。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、新規なゼラチン皮膜組成物及び易溶性硬質ゼラチンカプセルに関し、更に詳述すると、コハク化ゼラチンをベースにしたゼラチン原料にポリエチレングリコールを配合した、崩壊性に優れ、しかも脆化を防止することができるゼラチン皮膜組成物及び易溶性硬質ゼラチンカプセルに関する。

【０００２】

【従来の技術及び発明が解決しようとする課題】従来、硬質カプセル用素材としては、ゼラチンを基材とし、これにグリセリン又はソルビトール等の可塑剤を添加したものが知られている（以下、普通のゼラチンカプセルという）。

【０００３】しかしながら、このような素材から形成した普通のゼラチンカプセルには、そのカプセル内容物が例えば特殊な薬物である場合、特にマクロライド系抗生物質などのアルデヒド基を含むような薬物である場合には、これがカプセルを構成するゼラチンのアミノ基と容易に反応して巨大分子を形成することが認められ、この巨大分子の形成によりカプセルの不溶化という不都合が生じ、ひいては日本薬局方に定められた崩壊時間内に崩壊しないという欠点を招来することになる。特に、医薬品の製造許可申請に不可欠である４０℃，７５％ＲＨの条件で長期加速試験を行った場合、このような現象が生じることは大きな問題である。

【０００４】そこで、本発明者らは、このような欠点を改善するべく、カプセル基材としてコハク化ゼラチンを使用した易溶性硬質カプセルを先に提案している（特開昭６１－１８６３１４号公報）。

【０００５】しかしながら、このカプセルは、普通のゼラチンカプセルに比べて機械的強度が低く、薬物を充填した際又は経時保存時にカプセル皮膜が割れ易いといった欠点のために現時点では実用化が困難である。

【０００６】本発明は、上記事情に鑑みなされたもので、特殊な薬物を充填してもこれと反応して不溶化するなどの問題を生じることがなく、従って内容物が制限されず、種々の薬物に適用し得、しかも製剤化に耐え得る十分な機械的強度を有した硬質カプセルを製することができるコハク化ゼラチンをベースとしたゼラチン皮膜組成物及び該組成物により形成した易溶性硬質ゼラチンカプセルを提供することを目的とする。

【０００７】

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【課題を解決するための手段及び作用】本発明者らは、上記目的を達成するため鋭意検討を行った結果、内容薬物との反応により性質が変化するようなことがなく、種々の薬物に適用可能なコハク化ゼラチンをベースとする皮膜組成物にポリエチレングリコールを添加配合することにより、得られるコハク化ゼラチンカプセルの機械的強度を向上させることができることを見出した。即ち、コハク化ゼラチンを主成分とするゼラチン原料から硬質ゼラチンカプセルを製する際に、ゼラチン原料にポリエチレングリコール、好ましくは分子量１０００～２０００００のポリエチレングリコールを添加配合することにより、マクロライド系抗生物質などのアルデヒド基を有する薬物であっても不溶化してしまうようなことがなく、種々の薬物に良好に適応し得、しかも良好な崩壊性，溶解性を有し、かつ普通ゼラチンカプセルを凌駕するような良好な機械的強度を有する新規な硬質ゼラチンカプセルが得られることを見出し、本発明を完成したものである。

【０００８】なお、普通のゼラチンカプセルにポリエチレングリコールを配合することは既に知られている（特開平３－８０９３０号公報、特開平４－１５９２１８号公報）が、これらの提案は普通ゼラチンカプセルに関するものであって、コハク化ゼラチンをベースとする硬カプセルに関するものではなく、また上記ポリエチレングリコールの配合は普通ゼラチンカプセルにおける皮膜の低含有水分下での脆さの改善や、水分に対して不安定な薬物の充填製剤化を達成したり、普通ゼラチンカプセルが容器やカプセル同士で付着するのを防止することを目的としており、コハク化ゼラチンをベースとする硬カプセルの強度の向上を目的としたものでもない。コハク化ゼラチンをベースとする硬カプセルにポリエチレングリコールを配合することで、良好な崩壊性、溶解性、機械的強度を与え、コハク化ゼラチンベースの硬カプセルを種々の薬物に適応させて実用可能にしたということは本発明者の新たな知見に係るものである。

【０００９】従って、本発明は、５０～１００重量％がコハク化ゼラチンであるゼラチン原料を主成分とし、これにポリエチレングリコールを添加配合したことを特徴とするゼラチン皮膜組成物、及び、このゼラチン皮膜組成物から形成された易溶性硬質ゼラチンカプセルを提供するものである。

【００１０】以下、本発明につき更に詳しく説明する。本発明のゼラチン皮膜組成物は、上述したように、コハク化ゼラチンを主成分とするゼラチン原料にポリエチレングリコールを添加配合したものであり、また本発明の易溶性硬質ゼラチンカプセルは、この皮膜組成物から形成されたものである。

【００１１】ここで、上記コハク化ゼラチンを含むゼラチン原料は、コハク化ゼラチン単独でもコハク化ゼラチンと通常のゼラチンとの混合物であってもよいが、コハ

ク化ゼラチンは、普通ゼラチンより高価であるため、低コスト化が望まれる場合には、コハク化ゼラチンと通常のゼラチンとの混合物とすることが好ましく、この場合コハク化ゼラチンの含有量はゼラチン原料の５０重量％以上とされ、特に　７０重量％以上とすることが好ましい。コハク化ゼラチンの含有量が５０重量％未満であると、カプセル内容物の種類によってはカプセルの溶解性が劣化するおそれがある。なお、コハク化ゼラチンは、ゼラチンに無水コハク酸を反応させることにより容易に得ることができる。

【００１２】このゼラチン原料に添加配合するポリエチレングリコールは、特に制限されるものではないが、カプセルの溶解性及び機械的強度を顕著に向上させることができることから分子量１０００～２００００とすることが好ましく、更には分子量１０００、１５００、１５４０、４０００、６０００及び２００００から選ばれた１種又は２種以上のポリエチレングリコールを混合して用いることがより好ましい。

【００１３】このポリエチレングリコールの添加配合量は、特に制限されるものではないが、上記原料ゼラチンに対して１～３０重量％とすることが適当であり、１重量％未満であると得られるカプセルの機械的強度が十分に向上しない場合があり、一方３０重量％を超えると、ゼラチン溶液が白濁すると共に、その粘度が急激に低下してポリエチレングリコールを均一に混合させることが困難になり、カプセル成形時に均一なカプセル皮膜を得ることができなくなる場合がある。

【００１４】本発明のゼラチン皮膜組成物は、上記ゼラチン原料に上記ポリエチレングリコールを添加混合したものであるが、この場合、ポリエチレングリコールの添加混合方法は常法に従って行うことができる。具体的には、ゼラチン原料に水を加え、これを数時間自然放置して吸水膨潤させた後、ポリエチレングリコールを水溶液の状態で所定量添加混合し、粘度を調整してジェリー状のゼラチン組成物を得、これを常法により成形するという方法を例示することができる。なおこの場合、従来の硬質ゼラチンカプセルを製する場合と同様に、上記成分に加えて必要に応じてその他の添加剤、例えば薬事法又は食品衛生法等で指定された食用色素や二酸化チタンなどを添加することができる。

【００１５】なお、本発明のゼラチン皮膜組成物は、医薬品分野においてカプセル材料として好ましく利用されるものであるが、これに限定されず、医薬部外品、化粧品、食品、雑貨分野など種々の分野においても、容器材料や被覆材料として好適に使用し得、この場合その用途に応じて適宜な添加剤を添加することができる。

【００１６】また、このゼラチン皮膜組成物から形成された硬質ゼラチンカプセルは、アルデヒド基を有する薬物などの特殊な薬物を充填してもこれと反応して不溶化するなどの問題を生じることがなく、従って内容物が制限されず、種々の薬物に適用し得、しかも製剤化に耐え得る十分な機械的強度を有するものである。

【００１７】

【実施例】以下、実施例を示して本発明を具体的に説明するが、本発明は下記実施例に制限されるものではない。

【００１８】［実施例１］コハク化ゼラチン７．５ｋｇに精製水１３．５リットルを加え、約１～２時間自然放置して吸水膨潤させた。ゼラチンが十分に膨潤した後、６０℃に加温し、撹拌してゼラチンを均一に溶解させ、更にこのゼラチン溶液中に分子量４０００のポリエチレングリコールの５０重量％水溶液を１．５ｋｇ（１０重量％濃度）加えて撹拌し、その粘度を調整した後、常法により脱泡処理してカプセル成形用ジェリーを得た。このジェリーをカプセル成形装置に仕込み、サイズ２号のカプセルを成形した。

【００１９】［実施例２］分子量４０００のポリエチレングリコールに代えて分子量６０００のポリエチレングリコールを用い、このポリエチレングリコールの添加量を１重量％，３重量％，５重量％，１０重量％，２０重量％，３０重量％とした以外は、実施例１と同様にしてサイズ２号のカプセルを６種類成形した。

【００２０】次いで、上記実施例１及び２で得られたカプセルについて次の実験を行った。

［実験－１］（空カプセルの割れに対する評価）

上記実施例１及び２で得られたカプセルについて、その皮膜の含有水分量が１０％前後になるように調湿し、落錐試験法（４９．７ｇの重りを１０ｃｍの高さから落下させる）により割れ性を調べた。また、比較としてポリエチレングリコールを含まない従来のコハク化ゼラチン硬カプセル及び普通ゼラチン硬カプセル（日局カプセル）についても同様に割れ性を評価した。結果を表１に示す。なお、割れ性は各カプセル５０個について上記落錐試験を行い、割れの生じた個数により評価した。

【００２１】

【表１】

実施例１により製造したカプセル

	割れテスト	カプセル水分
本発明品	6個	8.7％
公知のコハク化ゼラチン硬カプセル	48個	10.1％
普通ゼラチン硬カプセル	31個	10.1％

実施例２により製造したカプセル

	PEGの添加量（重量W％）	割れテスト	カプセル水分
本発明品	1	11個	10.1％
	3	5個	10.0％
	5	0個	10.0％
	10	0個	9.8％
	20	0個	9.7％
	30	3個	9.5％
公知のコハク化ゼラチン硬カプセル		48個	8.7％
普通ゼラチン硬カプセル		31個	10.5％

【００２２】表１に示した結果から、本発明にかかる硬質ゼラチンカプセルは、公知のコハク化ゼラチン硬カプセル及び普通のゼラチン硬カプセルに比べて割れ難く、機械的強度に優れることが確認された。

【００２３】［実験－２］（マクロライド系抗生物質を充填した際の崩壊性）

実施例１で製造した本発明カプセルにミデカマイシンを２５０ｍｇ充填し、このカプセルについて日本薬局方第十二改正に記載の「カプセル剤」の項に従って崩壊性を試験した。即ち、製造直後のカプセルに内容物を充填し、６０℃，相対湿度７５％の条件で１０日間放置した後、崩壊試験を行い、試験開始からカプセルが開口するまでの時間を測定した。また、比較として普通ゼラチンカプセル（日局）についても同様に崩壊試験を行った。結果を表２に示す。なお、表中のデータはカプセル６個の平均値である。

【００２４】

【表２】

	本発明品	比較品
開始時	25秒	1分11秒
10日後	24秒	開口せず

【００２５】表２の結果から明らかなように、本発明のカプセルは日局ゼラチン硬カプセルに比べて崩壊性に優れ、しかもこの崩壊性は経時保存後においてもほとんど変化がなく、常に安定した崩壊性を示すことが認められる。

【００２６】［実験－３］（空カプセルの溶解性）

実施例１で製造した本発明カプセルについて日本薬局方第十二改正に記載の「カプセル」の項に従って溶状試験を行った。また、比較として普通ゼラチンカプセル（日局）についても同様に溶状試験を行った。結果を表３に示す。なお、表中のデータはカプセル５個の平均値である。

【００２７】

【表３】

	溶融時間
本発明品	1分19秒
比較品	3分41秒

【００２８】表３の結果から明らかなように、本発明にかかるカプセルは、日局ゼラチン硬カプセルに比べて溶解時間が短く溶解性に優れることが確認された。

【００２９】

【発明の効果】以上説明したように、本発明のゼラチン皮膜組成物により製した硬質カプセルはアルデヒド基を有する薬物など、特殊な内容物を充填しても経時崩壊遅延を生じることなく、かつ十分な機械的強度を有し割れ等の不都合も生じにくいものである。従って、マクロライド系抗生物質等の従来カプセル剤に製剤することが困難であった薬物をカプセル化することが可能となる。